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Alison L. Fife

Philadelphia College of Osteopathic Medicine, alisonfi@pcom.edu

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Is Ramelteon Effective in Improving Sleep Quality in Adult Patients with Mild to Moderate Obstructive Breathing Disorders?

Alison L. Fife, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences- Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Medicine
Philadelphia, Pennsylvania

December 20, 2013

Abstract

Objective: The objective of this selective EBM review is to determine whether or not ramelteon is effective in improving sleep quality in adult patients with mild to moderate obstructive breathing disorders.

Study Design: Review of three English studies published from 2007 to 2010; two randomized controlled studies and one randomized crossover study.

Data sources: The double blind randomized placebo controlled crossover trial, randomized double blind placebo controlled two way crossover study and double blind placebo controlled randomized controlled trial were found using PubMed.

Outcomes measured: Each of the studies measured the sleep quality in patients with either obstructive sleep apnea or COPD, which are both forms of chronic obstructive breathing disorders. Sleep quality was measured using a post sleep questionnaire on a seven-point Likert scale or by using the Pittsburgh Sleep Quality Index.

Results: Results from all three studies did not demonstrate any significant improvement in sleep quality in adult patients with mild to moderate obstructive breathing disorders.

Conclusions: Ramelteon has not been shown to improve sleep quality in adult patients with mild to moderate obstructive breathing disorders in the three studies reviewed.

Key Words: Ramelteon, Obstructive Breathing disorders, Sleep Apnea, COPD, sleep quality

INTRODUCTION

Patients with obstructive breathing disorders such as obstructive sleep apnea (OSA) and COPD can present many different ways. Patients can present with irregular and abnormal respiratory patterns during sleep, loud snoring, snorts during their sleep, as well as restlessness and disrupted sleep.¹ This paper evaluates a double blind randomized placebo controlled crossover trial, a randomized double blind placebo controlled two way crossover study and a double blind placebo controlled randomized controlled trial; comparing the efficacy of ramelteon in improving sleep quality in adult patients with mild to moderate obstructive breathing disorders.

This topic is relevant to the PA profession and patients because it is a common issue among Americans, ramelteon is cost effective, and a high number of patients seek healthcare for obstructive breathing disorders. It is estimated that there are 24 million Americans that have known airflow limitations.² Currently 20% of North Americans have OSA, which is defined as having an apnea hypopnea index (AHI) greater than five events per hour, and 2-9% have an AHI greater than five events per hour with at least one symptom that responds to treatment.³ There is not an exact estimate on how much is spent on all obstructive breathing disorders annually, but it is estimated around \$32 billion are spent on patients with COPD,⁴ and the costs for diagnosing and treating patients with OSA ranges between \$2 billion and \$10 billion dollars.⁵ There is not an exact estimate for how many patients with obstructive breathing disorders visited a healthcare facility for decreased sleep, however COPD accounts for 1.5 million emergency room visits, and 726,000 hospitalizations annually.⁴

There are many factors that can increase a patients chances of developing OSA, such as the size of the patients neck and the shape of their airway, swelling of a patients tonsils, smoking,

high blood pressure, risk factors of heart failure or stroke, and obesity.⁶ Continuous positive airway pressure (CPAP) is the main treatment used in patients with obstructive breathing disorders during sleep, but for patients who cannot tolerate or are not successful using the CPAP, the other options are limited to oral appliances or possible surgery.⁷

There are different treatments and therapies that are currently used to help improve sleep quality in patients with obstructive breathing disorders. The main therapy used in patients with obstructive breathing disorders is a CPAP device, which helps to keep airflow greater during sleep.⁷ Patients also can use oxygen concentrators to increase the amount of oxygen received during sleep. There are other oral appliances that can be used to help improve the sleep quality in patients with obstructive breathing disorders, such as mandibular repositioning appliances and tongue-retaining devices.⁷ Patients can also have surgery preformed to increase airflow during sleep. These surgeries include uvulopalatopharyngoplasty, somnoplasty and nasal surgery.⁷ Patients can also try to lose or manage their weight either medically with diet and exercise or with weight loss surgery. Patients can use oral medications such as Ipratropium, Prednisone, Albuterol, Metaproterenol, and Roflumilast to decrease the symptoms of their obstructive breathing disorder and help improve their sleep quality.⁷

Currently there is no cure for obstructive breathing disorders and decreased sleep, but the treatments listed above can help relieve the symptoms patient's experience and sleep quality. Ramelteon can be used on patients to help allow the patient to fall asleep more quickly in patients who have sleep-onset insomnia.⁸

OBJECTIVE

The objective of this selective EBM review is to determine whether or not ramelteon is effective in improving sleep quality in adult patients with mild to moderate obstructive breathing disorders.

METHODS

There are specific criteria that were used in the selection of participants for this study. The population for this study was patients over 19 years of age with mild to moderate obstructive breathing disorders. The intervention used was ramelteon. During this study the effectiveness of ramelteon was compared to a visually similar placebo. The outcome being measured for this study was the sleep quality in patients with mild to moderate obstructive breathing disorders based on the information obtained through the PQSI and Post sleep questionnaire. The studies used were a two double blind randomized placebo controlled crossover trials, and a double blind placebo controlled, randomized controlled trial comparing the effectiveness of ramelteon to a visually similar placebo and its effect on sleep quality.

The author used the keywords “ramelteon,” “obstructive breathing disorders,” and “sleep quality”, to search the PubMed database. All studies that were included were found on the PubMed database and were published in English. The articles were published in peer-reviewed journals. The articles were selected based on the relevance to the clinical question and if the study outcomes would make a difference to the patient which would make the study a POEM. Inclusion criteria used were studies that were randomized controlled or crossover trials published after 1996. Exclusion criteria included patients that had previously had surgery for obstructive breathing disorders, history of drug or alcohol abuse, currently using other sleep aids or fluvoxamine.

Statistics that were reported and used were p-values and confidence intervals.

Table 1- Demographics and Characteristics of Included Studies

Study	Type	# Pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	Intervention
Kryger ⁹ (2007)	RCT - cross over	26	19- 64 yrs	Men, nonpregnant or nonlactating women w/ diagnosis of mild to moderate obstructive sleep apnea (AHI \geq 5 and \leq 20 per hour of sleep) bedtime between 8:30 pm & 12:00 am w/ 4+ hours of sleep per night	Surgery for sleep apnea, use PAP device w/in 30 days, hypersensitivity to ramelteon, study recently using ramelteon, uncontrolled systemic illness, hepatitis, sleep or CNS medications that alter sleep, recent sleep schedule changes, history of psychiatric disorder/drug abuse, seizure, periodic limb movement or sleep disorders	0	Single dose of either 16 mg of ramelteon or placebo separated by a 5- or 12-day wash out period. Medication given 30 minutes before bedtime
Kryger ¹⁰ (2008)	RCT - cross over	26	51- 76 yrs	Clinical history of COPD, mild to moderate airflow limitation, post bronchodilator FEV ₁ change from baseline less than 12%, SaO ₂ over 85% during sleep for 99% recording period, no SaO ₂ less than 80%, SaO ₂ greater than 91% while awake, bedtime between 8:30 pm and 12:00 am.	Periodic leg movement arousal index >20, acute illness w/in 2 wks, disease/psychiatric disorder, history of drug/alcohol abuse w/in one year, shift work w/in 3 months, flown across 3+ time zones w/in 1 week, medication to affect sleep-wake function w/in 1 wk, RVH, right heart failure, acute or chronic respiratory failure, severe COPD, oxygen, hypercapnia, apnea hypopnea index >15, hematocrit >55%, weight loss program w/in 30 days	0	Single dose of either 16 mg of ramelteon or placebo separated by a 5- or 12-day wash out period. Medication given 30 minutes before bedtime
Goone-ratne ¹¹ (2010)	RCT	21	>60 yrs	Patients over 60 years old with a diagnosis of sleep apnea syndrome with a minimum of AHI of 5 events/hour.	Restless leg syndrome, periodic limb movement disorder, severe emphysema, alcohol abuse, cognitive or liver abnormalities, prior use of CPAP, actively use fluvoxamine/sedative hypnotics	6	8 mg of Ramelteon or placebo given 30 minutes before their bedtime for 30 days

OUTCOMES MEASURED

The outcomes in the studies from Kryger were used to assess sleep quality in subjects with COPD or the diagnosis of mild to moderate obstructive sleep apnea.^{9,10} These studies used a post-sleep questionnaire, which was measured using a seven-point Likert scale.^{9,10} The outcomes that were addressed in the Gooneratne et al study were the sleep quality in patients with obstructive sleep apnea.¹¹ This was measured by using the Pittsburgh Sleep Quality Index (PSQI), which assesses sleep quality and its changes in insomnia.¹¹ A higher PSQI indicated a worse sleep quality the subjects had encountered. The PSQI is rated on a 21 point score from a minimum score of 0 to a maximum score of 21.¹² This study also originally asked the subjects to complete an at-home sleep diary, however less than half of the participants completed the sleep diary so it was excluded from the results.¹¹

RESULTS

All three articles compared the use of ramelteon with a placebo for improving sleep quality in adult patients with mild to moderate obstructive breathing disorders. Kryger et al⁹ is a double blind randomized placebo controlled crossover trial. Kryger et al¹⁰ is a randomized double blind placebo controlled two way crossover study. Gooneratne et al¹¹ is a double blind, placebo controlled, randomized controlled trial. Each article was presented as continuous data.^{9,10,11}

Kryger et al conducted a trial that involved 26 adults aged 51-76 with clinical history of COPD or mild to moderate airflow limitation.¹⁰ This study excluded patients with periodic leg movement arousal index >20, acute illness within 2 weeks, disease or psychiatric disorder, history of drug or alcohol abuse within one year, shift work within 3 months, patients that have flown across three or more time zones within one week, or if the patients have taken medication to affect their sleep-wake function within one week.¹⁰ Patients were also excluded if they had right ventricular hypertrophy, right heart failure, acute or chronic respiratory failure, severe

COPD, need for nocturnal oxygen, hypercapnia, apnea hypopnea index >15, hematocrit >55% or if they have participated in a weight loss program within 30 days.¹⁰ The patients were given a single dose of either 16 mg of ramelteon or a placebo, separated by a 5 or 12-day wash out period and then the patients received the other. The medication was given 30 minutes before the participant's bedtime. The participants used a seven-point scale post-sleep questionnaire to measure their sleep quality throughout the trial.¹⁰ The ramelteon mean difference from baseline was 3.5 and the mean difference for the placebo from baseline was 3.6.¹⁰ The mean difference between the ramelteon and placebo was 0.10 (Table 2).¹⁰ There was no statistical significance found with sleep quality in the subjects with the reported p-value ($p=0.690$) and a 95% CI of (-0.5, 0.4) (Table 3).¹⁰

Kryger et al was a double blind, placebo controlled, randomized crossover trial.⁹ This trial excluded patients who have received surgery for sleep apnea, patients that have used positive airway pressure devices within 30 days, had a hypersensitivity to ramelteon in any previous study using ramelteon.⁹ It also excluded patients with uncontrolled systemic illness, hepatitis, other sleep or CNS medications that can alter sleep, with any recent sleep schedule changes, history of psychiatric disorders or drug abuse, patients with history of seizures, periodic limb movement disorders or other sleep disorders.⁹ In this trial 26 adults between 19 and 64 years of age were given a single dose of either 16 mg of ramelteon or a placebo 30 minutes before their bedtime at a sleep center, followed by a 5 or 12-day washout period and then the patients were given the other.⁹ The medication was given 30 minutes before the participant's bedtime. The participants sleep quality was assessed with a post-sleep questionnaire that used a seven-point Likert scale, ranging from "excellent" to "extremely poor."⁹ The ramelteon mean difference from baseline was 3.8 and the mean difference for the placebo from baseline was 3.7.⁹

The mean difference between the ramelteon and placebo was 0.10 (Table 2).⁹ There was no statistical significance found with sleep quality in the subjects with the reported p-value ($p=0.668$) and a 95% CI of (-0.5 , 0.7) (Table 3).⁹

Gooneratne et al was a double blind, placebo controlled, randomized control trial.¹¹ This trial excluded patients with restless leg syndrome, periodic limb movement disorder, severe emphysema, alcohol abuse, cognitive or liver abnormalities, prior use of CPAP, and patients actively using fluvoxamine or sedative hypnotics.¹¹ In this trial the participants were given 8 mg of Ramelteon or a placebo 30 minutes before their bedtime. This study used intention to treat comparisons to decrease the chance of there being bias in excluding subjects from the analyzed groups.¹¹ During the study six participants (22.2%) were lost and no worst-case analysis was performed.¹¹ Of the 27 original participants chosen, 8 of the subjects using ramelteon and 13 of the subjects using the placebo were analyzed.¹¹ The participants sleep quality was measured with the Pittsburgh Sleep Quality Index.¹¹ The subjects were given a pre and post intervention PSQI.¹¹ The subjects that received ramelteon had a mean difference from baseline of 10.45 and the subjects that received the placebo had a mean difference from baseline of 9.35 (Table 2).¹¹ There was a mean difference of 1.11 points between the ramelteon and placebo groups (Table 2).¹¹ There was no statistical significance found with sleep quality in the subjects with the reported p-value ($p=0.5$) and a 95% CI of (-1.20, 0.57) (Table 3).¹¹

Table 2- Efficacy of ramelteon when compared to placebo

Study	Group	Mean (SD) difference
Kryger ⁹	Ramelteon	3.8 (0.25)
	Placebo	3.7 (0.25)
Kryger ¹⁰	Ramelteon	3.5 (0.2)
	Placebo	3.6 (0.2)
Gooneratne ¹¹	Ramelteon	10.45
	Placebo	9.35

Table 3- Efficacy of ramelteon in improving sleep quality in mild to moderate obstructive breathing disorders

Study	95% CI	p-value
Kryger ⁹	(-0.5 , 0.7)	0.668
Kryger ¹⁰	(-0.5 , 0.4)	0.690
Gooneratne ¹¹	(-1.20 , 0.57)	0.5

Some adverse effects were noted by the Gooneratne et al study. A total of four adverse effects occurred with ramelteon including gastrointestinal-diarrhea, dermatologic- skin ulcer, pulmonology- paranasal reaction, musculoskeletal fracture after being hit by a bicyclist.¹¹ A total of two adverse effects occurred with the placebo including abdominal pain and gastrointestinal- nausea.¹¹ All these adverse effects were thought to be unrelated to the drug during the treatment and it was noted that none of the adverse events were severe.¹¹ The adverse effects noted during Kryger et al with ramelteon were two headaches and one urinary tract infection.⁹ The two headaches were noted as possibly related but resolved with acetaminophen and the urinary tract infection was noted as unrelated and resolved spontaneously.⁹

DISCUSSION

Ramelteon works on MT₁/MT₂ receptors, and these receptors are involved in the circadian rhythm, which effects the sleep-wake cycle.⁹ Ramelteon is a melatonin receptor agonist and has been shown to have little effect on sleep apnea severity.¹¹ Ramelteon is available to patients with a prescription, which could prevent some patients from trying this medication since other similar medications such as melatonin are available over the counter.¹³ The cost of ramelteon, brand name Rozerem, is around \$250.00 per month without insurance. Due to the higher cost, some patients may not be able to financially afford rameleteon.¹³ Several contraindications and concerns are taken into consideration when a patient is using ramelteon.¹³ Patients with a history of angioedema when previously using ramelteon should not re-challenge,

and it is also contraindicated with the use of fluvoxamine.¹³ It is also important to take ramelteon immediately prior to the patient's bedtime due to the rapid onset and cause of patients to become drowsy.¹³

All three studies analyzed showed no significant improvement in sleep quality in adult patients with mild to moderate obstructive breathing disorders when comparing ramelteon to the use of a placebo. The small sample sizes in all three studies, between 21 and 26 subjects, may not accurately represent the total population of patients with obstructive breathing disorders. In Gooneratne et al there was a 50% adherence to the APAP which could cause the patients to have a poorer sleep quality due to reasons other than the study drug.¹¹ Having subjects with an age range of 19 and older allows for less precision, as sleeping habit and sleep quality change over time. The younger subjects and older subjects may have very different baselines making it difficult to compare the two in one study. Although the studies using a crossover design did have a wash out period between interventions, a carry-over effect may still have been present in some patients.

CONCLUSION

Based on this systematic review and the studies analyzed, ramelteon is not effective in improving sleep quality in adult patients with mild to moderate obstructive breathing disorders. These three studies show no statistically significant data to support the improvement of sleep quality. No severe adverse effects were noted in any of the three studies. Although the studies analyzed did not show that ramelteon improved sleep quality, future studies could be performed with larger populations to more accurately represent the population with obstructive breathing disorders. In the studies analyzed above, both Kryger et al studies monitored the subjects overnight, while Gooneratne et al sent the participants home with either the ramelteon or

placebo.^{9,10,11} In future studies, patients should all receive their medications at a sleep center, which would allow them to be monitored taking the medication, using the APAP machine and improve the completion of post-sleep questionnaires.

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